United States Patent Office

3,185,679
Patented May 25, 1965

3,185,679

AZEPINE DERIVATIVES

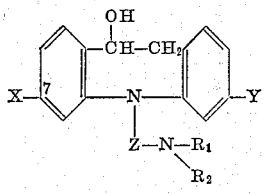
Walter Schindler, Riehen, and Hans Blattner, Basel, Switzerland, assignors to Geigy Chemical Corporation, New York, N.Y., a corporation of Delaware

No Drawing. Filed Dec. 2, 1963, Ser. No. 327,507
Claims priority, application Switzerland, Dec. 6, 1962, 14,326/62
2 Claims. (Cl. 260—239)

This invention relates to new azepine derivatives with valuable pharmacological properties, as well as a process for the production thereof.

More particularly, this invention relates to a new iminodibenzyl type azepine derivative which is characterized by possessing substituents in the 7- as well as in the 10-position, and which is distinguished by an unexpected combination of pharmacological properties.

Compounds of the general formula



(I)

wherein

X and Y independently of each other represent hydrogen or chlorine,

Z represents a straight or branched chained alkylene radical with 2 to 4 carbon atoms,

R_1 represents a lower alkyl radical or a hydrogen atom, and

R_2 represents a lower alkyl radical,

have not been known up to now. It has now been found that such compounds and their salts with inorganic or organic acids have valuable pharmacological properties, in particular reserpine-antagonistic, serotonin-antagonistic and anti-cholinergic activity, and are suitable, for example, for the treatment of mental disorders, particularly of depressions. They may be administered orally or, in the form of aqueous solutions of their salts, also parenterally.

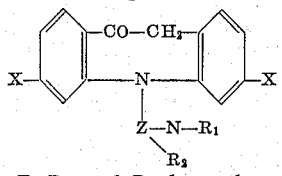
Especially the compound falling under Formula I which possesses as sole substituents, apart from the hydroxyl group in 10-position, a chlorine atom in 7-position and the γ-dimethylaminopropyl radical in 5-position, is distinguished from other hydroxy- and chloro-substituted iminodibenzyls by its pharmacodynamic spectrum which contains a pronounced reserpine-antagonistic component with contributory serotonin-antagonistic and anti-cholinergic activities, while there is practically no antihistaminic component present. This compound is, therefore, especially indicated for use in the treatment of depressions where no accompanying calmative component in the spectrum of the active agent is desired.

This spectrum of the above-described 5-(γ-dimethylamino-propyl)-7-chloro-10,11-dihydro-5H - dibenz [b,f]-azepin-10(11H)-ol is particularly unexpected, since the corresponding 7-chloro-10-keto analog possesses only much weaker reserpine-antagonistic activity and practically no anti-cholinergic activity or no serotonin-antagonistic activity, but a considerable antihistaminic effect, while the 7-unsubstituted 10-keto analog possesses equally inferior reserpine-antagonistic activity as the 7-chloro-10-keto compound, also a much weaker serotonin-antagonistic property than the new 7-chloro-10-hydroxy-derivative, practically no anticholinergic activity, however, just as the 7-chloro-10-keto analog, a relatively strong antihistaminic component in its pharmacodynamic spectrum. It

should also be noted that introduction of a methyl group in 10-position into the corresponding 7-chloro-5-(γ-dimethylamino-propyl)-10,11 - dihydro-5H-dibenz[b,f] azepine does, indeed, practically eliminate the antihistaminic component from the pharmacodynamic spectrum of the latter, but also, simultaneously, eliminates the beneficial serotonin-antagonistic effect of the latter and seriously reduces the anti-cholinergic activity to be found in the spectrum of the 10-unsubstituted 7(3)-chloro compound.

In the compounds of the general Formula I, X is, for example, hydrogen or a chlorine atom in the 7-position, and Y is hydrogen or a chlorine atom in the 3-position. Z is, for example, an ethylene, propylene, trimethylene or 2-methyl-trimethylene radical. Lower alkyl radicals R_1 and R_2 are preferably methyl radicals; further, for example, they can be ethyl, n-propyl, isopropyl, n-butyl or isobutyl radicals.

The new compounds of Formula I are produced by reducing a compound of the general formula



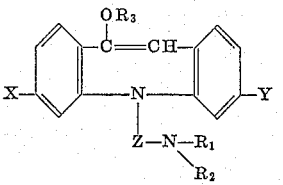
(II)

wherein X, Y, Z, R_1 and R_2 have the meanings given above.

The reduction of the carbonyl group in the 10-position to the hydroxy-methylene group necessitates an equimolar amount of hydrogen. For example, compounds of the general Formula II are reduced by means of a complex hydride, in particular lithium aluminum hydride, in an ether-type solvent such as diethyl ether, dibutyl ether, tetrahydrofuran or dioxan, or by means of sodium borohydride, for example in methanol, at room temperature or at a moderately raised temperature. Also, the compounds of Formula II can be reduced by means of catalytically activated hydrogen, for example, in the presence of Raney nickel under increased pressure and at a raised temperature in a lower alkanol or in dioxan as solvent, or in the presence of a noble metal catalyst such as palladium on charcoal or on an alkaline earth metal carbonate.

Starting materials of the general Formula II are known or can be produced in an analogous manner, as described, for instance, in French Patent 1,300,731, issued July 2, 1962, and in British patent application 943,277, published February 4, 1963.

They are produced by hydrolysis of compounds of the general formula



(III)

wherein

R_3 represents a lower alkyl radical, and (X, Y, Z, R_1 and R_2 have the meanings given above,

for example, by heating in dilute hydrochloric acid. Compounds of Formula III in which R_1 is not hydrogen can be produced by condensing by means of sodium amide or another active condensing agent, while heating in an inert organic solvent such as, for example, toluene, 10-alkoxy-5H-dibenz[b,f]azepines which may be substituted corresponding to the definition of X and Y, with dialkylaminoalkyl halides. Compounds having a hydrogen atom as R_1, are obtained from the above-mentioned reaction products by reacting them, for example,